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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/905,591	07/13/2001	Keiya Ozawa	50026/012004	4282

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EXAMINER	
SISSON, BRADLEY L	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 08/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/905,591	OZAWA ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7,18,34,35,37,38,40,41,44 and 45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/05, 3/06, 8/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 7, 18, 34, 35, 37, 38, 40, 41, 44 and 45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Attention is directed to the decision in *University of Rochester v. G.D. Searle & Co.* 68 USPQ2D 1424 (Fed. Cir. 2004) at 1428:

> To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. Vas-Cath, 935 F.3d at 1563; see also Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572 [41 USPQ2d 1961] (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention"); In re Gosteli, 872 F.2d 1008, 1012 [10 USPQ2d 1614] (Fed. Cir. 1989) ("the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed"). Thus, an applicant complies with the written-description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572.

3. A review of the disclosure finds the following examples:

a. Example 1, "Constructing the chimeric G-CSF receptor/estrogen receptor gene (a selective amplification gene)," pages 9;

b. Example 2, "Isolation of Ba/F3 cells into which was introduced the chimeric G0CSF receptor/estrogen receptor gene, which is a selective amplification gene," pages 9-11;

c. Example 3, "Analysis of cell proliferation by esterdiol," page 11;

d. Example 4, "Construction of the IRES-CD24 expression plasmid," pages 11-12;

e. Example 5, "Intracellular expression of CD24," pages 12-13; and

f. Example 6, "Progenitor assays," pages 13-15.

4. Further review of the specification finds that the method is to be limited to the selective proliferation of hematopoietic stem cells, not just any and all manner of "blood cells," e.g., anucleated cells such as red blood cells, which are encompassed by the claims. Additionally, the specification stipulates that a vector must be present in the cell and that the vector be one capable of expressing the desired fusion protein. The claimed method is not so limited and a review of the specification fails to find support for the method now claimed.

5. The claimed method fairly encompasses *in vivo* gene therapy, yet the specification fails to provide an adequate written description of just how such a method is to be practiced for any life form. Indeed, none of the examples teach gene therapy, much less provide art-accepted models for conducting such a method on humans.

6. As can be seen above, none of the examples are directed to the selective proliferation of a cell, e.g., gene therapy, in a mixed/heterogeneous assay. A review of the disclosure fails to find an adequate written description of the reagents used to practice the claimed method. Also not apparent is a written description of the best mode contemplated by applicant for practicing the invention.

7. It appears that applicant is attempting to satisfy the written description requirement of 35 USC 112, first paragraph, through obviousness. Obviousness, however, cannot be relied upon for satisfaction of the written description requirement. In support of this position, attention is directed to the decision in *University of California v. Eli Lilly and Co.* (Fed. Cir. 1997) 43 USPQ2d at 1405, citing *Lockwood v. American Airlines Inc.* (Fed. Cir. 1997) 41 USPQ2d at 1966:

> Recently, we held that a description which renders obvious a claimed invention is not sufficient to satisfy the written description requirement of that invention.

8. For the above reasons, and in the absence of convincing evidence to the contrary, claims 7, 18, 34, 35, 37, 38, 40, 41, 44 and 45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Response to argument

9. At pages 12-16 of the response received 20 March 2006 the rejection of claims under 35 USC 112, first paragraph, is traversed. Attention is directed to the six examples, with special attention being directed to Example 6.

10. Said argument and the specification, including Example 6, have been considered and have not been found persuasive towards the withdrawal of the rejection. It is noted that the claimed invention fairly encompasses the 'selective proliferation" of any and all manner of blood cells. Neither the specification nor the example teaches how one would be able to select one form of blood cell over that of another when the protein is administered to an individual or to a mixed population of blood cells. A review of Example 6 finds the disclosure therein not commensurate in scope with that of the now claimed invention. As found therein, 6-week-old

mice were injected with 5-fluorouracil, followed with extraction of bone marrow, with culture of cells in the presence of IL6 and SCF and cultured with "vMXGCRER" or "vMXGCR Δ(5-195)/ER" retrovirus constructs. It is noted with particularity that the claimed method does not recite the use of IL6 and SCF with any retroviral construct, much less the two recited in the example. Further, the example clearly does not teach administering the recombinant protein to cells, be it ex vivo or in vivo, as is presently encompassed by the claims. In short, the disclosure is not commensurate with the scope of the claims, and does not reasonably suggest that applicant was in possession of the invention at the time of filing. Attention is directed to the decision of *Vas-Cath Inc. v. Mahurkar* 19 USPQ2d 1111 (CAFC, 1991):

> This court in *Wilder* (and the CCPA before it) clearly recognized, and we hereby reaffirm, that 35 USC 112, first paragraph, requires a "written description of the invention" which is separate and distinct from the enablement requirement. The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the "applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

11. For the above reasons, and in the absence of convincing evidence to the contrary, claims 7, 18, 34, 35, 37, 38, 40, 41, 44 and 45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Claims 7, 18, 34, 35, 37, 38, 40, 41, 44 and 45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

The quantity of experimentation necessary,

The quantity of experimentation required is vast with little if any reasonable expectation of success.

The amount of direction or guidance presented,

The amount of direction provided is very limited, and then not commensurate with the scope of the claims. Indeed, none of the six examples provided set forth reaction conditions and starting materials required to practice the full scope of the now-claimed invention.

The presence or absence of working examples,

12. A review of the disclosure finds the following examples:

g. Example 1, "Constructing the chimeric G-CSF receptor/estrogen receptor gene (a selective amplification gene)," pages 9;

h. Example 2, "Isolation of Ba/F3 cells into which was introduced the chimeric G0CSF receptor/estrogen receptor gene, which is a selective amplification gene," pages 9-11;

i. Example 3, "Analysis of cell proliferation by esterdiol," page 11;

j. Example 4, "Construction of the IRES-CD24 expression plasmid," pages 11-12;

k. Example 5, "Intracellular expression of CD24," pages 12-13; and

l. Example 6, "Progenitor assays," pages 13-15.

The nature of the invention,

The invention relates to both *ex vivo* and *in vivo* gene therapy in any life form where selective proliferation of blood cells is desired.

The state of the prior art,

The state of the prior art is one where much difficulty has been encountered.

The predictability or unpredictability of the art, and

While much research has been and is continuing in this area, the art is recognized s being rife with serious issues of enablement. In support of this position attention is directed to the January 14 2003 letter from NIH Director Patterson, M.D., regarding adverse experience with gene therapy in blood cells using cytokine receptors. It is noted that in the nearly seven years since the filing date of the instant application, the ability to effectively treat blood cells, much less a broader genus of cells, in just one life form, has been met with much difficulty, and that the NIH was recommending that the such investigations be "discontinued." As noted in *In re Fisher* 166 USPQ 18 (CCPA, 1970):

> In cases involving predictable factors, such as that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved. (Emphasis added)

Attention is also directed to the July 2005 publication of Lorico et al., (published some 9 years after the applicant's priority date) state in part:

> In most experimental gene therapy protocols involving stem/progenitor cells, only small fractions of cells, often therapeutically inadequate, can be transfected and made to express the therapeutic gene.

It is noted that the claimed method fairly encompasses the selective proliferation of hematopoietic stem cells.

Attention is also directed to the abstract of Larghero et al., who teach gene therapy is problematic in patients who have depleted numbers functional hematopoietic progenitor cells, e.g., patients suffering from Fanconi Anemia, who have bone marrow failure and impaired stem cell compartment renewal. Larghero et al., conclude that "collecting functional hematopoietic cells for gene therapy trials could be difficult to achieve from classical FA patients."

The breadth of the claims.

As presently worded, the claims fairly encompass the selective proliferation of any population of blood cells where no gene therapy is used. The specification clearly does not teach such an embodiment.

Alternatively, the claims fairly encompass both *ex vivo* and *in vivo* gene therapy, where the host is any animal, including humans, and any blood cell is the target of selective proliferation. Example six is arguably the most relevant, yet the example recites numerous critical limitations not recited in the pending claims. As found therein, 6-week-old mice were injected with 5-fluorouracil, followed with extraction of bone marrow, with culture of cells in the presence of IL6 and SCF and cultured with "vMXGCRER" or "vMXGCR Δ (5-195)/ER" retroviral constructs. It is noted with particularity that the claimed method does not recite the use of IL6 and SCF with any retroviral construct, much less the two recited in the example.

13. In view of the breadth of scope clamed, the limited guidance provided, the unpredictable nature of the art to which the claimed invention is directed, and in the absence of convincing evidence to the contrary, the claims are deemed non-enabled by the disclosure. Therefore, and in

the absence of convincing evidence to the contrary, claims 7, 18, 34, 35, 37, 38, 40, 41, 44 and 45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

Response to argument

14. At pages 16-18 of the response of 20 March 2006, argument is presented that no evidence has been presented by the Office showing non-enablement of the claimed invention. For reasons set forth above, this argument has not been found persuasive.

15. At page 18, bridging to page 19 of said response attention is directed to the Declaration under 37 CFR 1.131 of Dr. Yasuji Ueda, and the exhibit of Hara et al., which was published in 2004.

16. As an initial matter, it is noted that declarant is a co-inventor of the claimed invention and as such is not a disinterested third party.

17. The question of enablement is not whether one could resolve the matter today, but rather, whether applicant had fully enabled the full scope of the claimed invention at the time the invention was made, which for purposes of examination, is considered to be March 5, 1996. It is noted with particularity that no papers have been filed showing what work applicant performed prior to filing in the interest of fulfilling the enablement requirement. While an exhibit has been made, the Hara et al., publication is not reflective of the level of enablement at the time of filing as it was published some 8 years post filing. It is noted with particularity that the article, which is reflective of the body of work up to the time of publication in 2004, states "Hematopoietic stem cell gene therapy has not provided clinical success in disorders such as chronic granulomatous disease (CGD), where genetically corrected cells do not show selective advantage

in vivo." Such historical overview, which clearly spans the time of applicant's filing, as well as some 8 years post filing, clearly teaches of the lack of success (non-enablement) in claimed area.

18. In considering the disclosure of Hara et al., as a whole, it is noted that the experimental conditions employed are not commensurate with the instant disclosure. Further, the method steps performed by Hara et al., are not recited in the present claims. Accordingly, and in the absence of convincing evidence to the contrary, the declaration has not been found persuasive towards the withdrawal of the rejection.

Conclusion

19. Objections and/or rejections which appeared in the prior Office action and which have not been repeated hereinabove have been withdrawn.

20. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

21. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

23. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

24. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

B. L. Sisson

Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS